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L6 ANSWER 12 OF 13 USPATFULL on STN

TI **Cyclosporin**-containing pharmaceutical composition

AB The present invention relates to a pharmaceutical composition containing **cyclosporin**. More specifically, the present invention relates to a pharmaceutical composition containing **cyclosporin**, an oil component, a hydrophilic cosurfactant consisting of **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer, and a **surfactant**. The composition of the present invention is characterized in that it can be dissolved in an external phase such as water, artificial gastric juice and intestinal juice, etc. to form a self-**emulsion** with mild stirring and therefore, by appropriately adjusting the constitutional ratio of each component the diameter of particles in the inner phase of the **emulsion** thus formed can be readily controlled to 100 nm or below. The composition of the present invention can be formulated. . . sealed with gelatin bending at the conjugated portion, oral liquid preparations, etc. When the composition of the present invention using **propylene carbonate** or its mixture with polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature is formulated into the soft capsule,. . .

SUMM The present invention relates to a pharmaceutical composition containing **cyclosporin**. More specifically, the present invention relates to a pharmaceutical composition containing **cyclosporin**, an oil component, a hydrophilic cosurfactant consisting of **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer, and a **surfactant**. The composition of the present invention is characterized in that it can be dispersed in an external phase such as water, artificial gastric juice and intestinal juice, etc. to form it self-**emulsion** with mild stirring and therefore, by appropriately adjusting the constitutional ratio of each component the diameter of particles in the inner phase of the **emulsion** thus formed can be readily controlled to 100 nm or below.

SUMM **Cyclosporin** is a high molecular peptide compound (molecular weight 1202) consisting of 11 amino acids and has a potent immunosuppressive activity by inhibition of growth and differentiation of T cells. Therefore, **cyclosporin** has been used for suppression of immunological rejection of the patients, which may be caused by organ and tissue transplantation, for example, transplantation of kidney, liver, heart, bone marrow, pancreas, skin, cornea, etc. In addition, **cyclosporin** has also been used for suppression of autoimmune diseases, especially inflammatory diseases such as rheumatoid arthritis.

SUMM **Cyclosporin** has a unique structure in which among 11 amino acids 7 amino acids are in the N-methylated form. In addition, **cyclosporin**, having a cyclic, symmetric structure, has a very low polarity and therefore, is very slightly soluble in water (0.04 mg/ml H.sub.2 O, 25° C.). Due to such a low water-solubility of **cyclosporin**, the bioavailability of **cyclosporin** is as very low as 30% or less. In addition, the absorption of such insoluble compound may be greatly influenced by bile juice secretion and fat amount in food. In the case of **cyclosporin**, it has been reported that the difference of absorption between each individual is as very great as about 5-50%.

SUMM When **cyclosporin** is administered, 10 to 27% of the absorbed drug is subjected to the first pass effect in liver and the. . . distribution half-life is 0.7 to 1.7 hour and the excretion half-life is 6.2 to 23.9 hours. Such pharmacokinetic parameters of **cyclosporin** show a great variation between each individuals

depending on secretion of bile juice, condition of patient and kind of transplanted organs. In addition, **cyclosporin** has a very low therapeutic index and frequently shows renal toxicity as the typical side effect. That is, **cyclosporin** shows renal side effects such as reduction of glomerular filtration, increase in proximal renal tubular reabsorption, etc. A form of chronic progressive **cyclosporin**-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidney. Therefore, in U.S.A. **cyclosporin** is classified as a group of drugs which should be subjected to a periodic therapeutic drug monitoring (TDM).

SUMM Since **cyclosporin** has such specific properties, that is, a very slight solubility, a low bioavailability and a great variation in absorption between. . . each individual, a great dosage unit and a narrow therapeutic index, and the unstable patient condition to be treated with **cyclosporin**, it is very difficult to establish the optimum drug dosage regimen for survival of transplanted patient by maintanance of efficient. . . develop an improved pharmaceutical formulation. Such study of pharmaceutical formulation has been mainly concentrated on the means which can solubilize **cyclosporin**. Typical example of such means includes the use of liposome, microsphere, the mixed solvent system consisting of general vegetable oil and **surfactant**, etc., the formation of powdery composition using adsorption, inclusion complex, solid dispersion, etc., and the other numerous formulations.

SUMM The oral preparation containing **cyclosporin** as the main active ingredient has been commercialized in the form of a solution or soft capsule. Recently, the microemulsion **preconcentrate** composition containing **cyclosporin** has also been formulated and commercialized in the form of soft capsule.

SUMM . . . cosmetic application. General microemulsion is a thermally stable and optically transparent preparation comprising two or more immiscible systems formed by **surfactants** and has some advantages that it has very low surface tension and small particle size to show high absorption and permeation properties. However, since the formation of microemulsion requires more **surfactant** than that used for formation of general **emulsion**, when the microemulsion is administered or applied for a long period, the mucosal irritation to be caused by each component. . .

SUMM . . . water-in-oil microemulsion disclosed in U.S. Ser. No. 818,965, it is described that when the microemulsion is prepared by selecting the **surfactant** and the cosurfactant which is more hydrophilic than the **surfactant**, and then adding the **surfactant** and the oil component to the external phase in which the cosurfactant is dissolved, the transparent microemulsion can be efficiently obtained under more stable and variable conditions. In addition, this patent also reports the microemulsion **preconcentrate** formulation which is prepared by a method that the very slightly soluble drug is dissolved in hydrophilic cosurfactant such as. . . chain hydrocarbons and then the oil solution produced by mixing the drug solution as prepared above with oil component and **surfactant** is added to the external phase to form the microemulsion.

SUMM In the case of **cyclosporin** as the very slightly soluble drug, U.S. Pat. No. 4,388,307 discloses the oral liquid preparation prepared by using oil, **surfactant** and ethanol as the hydrophilic solvent. This preparation is in the form of microemulsion **preconcentrate** and therefore, before it is administered per oral, it must be diluted with water. Accordingly, it is very difficult to. . . the accurate dosage and as a result, it is impossible to actually apply to the patient who must receive the **cyclosporin** therapy during his all life since it is uncomfortable to carry.

SUMM In order to improve such disadvantages involved in the liquid preparation, it has been proposed that the microemulsion

preconcentrate is formulated in the form of soft capsule. However, in case of the **cyclosporin** soft capsule containing ethanol as hydrophilic component, this capsule preparation must contain a large amount of ethanol for sufficient solubilization of **cyclosporin**. However, since ethanol permeates the gelatin shell of the capsule to volatilize even at normal temperature, the content of ethanol. . . result, when the capsule preparation is stored at high temperature or at normal temperature for long period, the crystallization of **cyclosporin** may be caused. Thus, the change in constitutional ratio of the composition caused by the change of ethanol content and the crystallization of **cyclosporin** result in a great variation in the bioavailability of **cyclosporin** and therefore, it is impossible to obtain the reliable uniform therapeutic effect. In this condition, in an effort to prevent. . . the change of ethanol content in course of time. Therefore, this also results in a great variation in bioavailability of **cyclosporin** and may contribute to the manufacturing price increase.

SUMM As one method for improving such disadvantages, Korean Patent Application No. 94-13945 discloses a **cyclosporin** soft capsule composition (trade name: Neoplanta®) using dimethylisosorbide as a hydrophilic cosurfactant. In this patent, it is described that since. . .

SUMM As mentioned above, the conventional microemulsion composition requires more **surfactant** than the general **emulsion** and therefore, in the case of drug which is continuously administered to the patient during his whole life after transplantation, for example, **cyclosporin**, the toxicity due to long term administration of solvent and **surfactant** used in the preparation of microemulsion must be considered. In this connection, the LD.sub.50 value of each **surfactant** used in **cyclosporin** formulations in the prior art is as follows: dimethylisosorbide 5.63 ml/kg (rat, per oral), Cremophor RH40>16 g/kg (rat, per oral),. . . oral), toluene 7.53 g/kg (rat, per oral), isopropanol 5.8 g/kg (rat, per oral), butanol 4.36 g/kg (rat, per oral), and **propylene carbonate**, which is used in the present invention as the solvent, 29 g/kg. In considering the LD.sub.50 values as above, the. . . may cause some problems. Furthermore, according to this patent dimethylisosorbide is used in an amount 4 times as much as **cyclosporin** on the basis of weight. This must be seriously considered in view of the fact that this drug is administered. . .

SUMM In addition, in case of the **cyclosporin** soft capsule composition using dimethylisosorbide, it is disadvantageous that obtain the comparable drug absorption to the commercial product Sandimmun Neoral® and the solubilizing effect sufficient to prevent the precipitation of **cyclosporin** the solvent is used in a relatively larger amount than the active ingredient. This means an increase in the unit dosage. That is, the hydrophilic cosurfactant, i.e. dimethylisosorbide is used in the 4 times amount per unit weight of **cyclosporin**. Therefore, the total weight of the unit dosage form of Neoplanta® capsule containing 100 mg of **cyclosporin** is about 1270 mg which is about 1.2 times as much as the weight of unit dosage form of the. . .

SUMM Thus, the present inventors have studied numerous **cyclosporin** preparations using various hydrophilic cosurfactants, oils and **surfactants** in view of their stability and bioavailability to prepare the **cyclosporin**-containing composition which makes up for various disadvantages involved in the pharmaceutical preparations of the prior art and is suitable for. . . low toxicity and small dosage unit. As a result, we have identified that when as the hydrophilic cosurfactant in the **cyclosporin**-containing composition **propylene carbonate**, which is a pharmaceutically acceptable solvent, or a mixture of **propylene carbonate** with polyoxyethylene-polyoxypropylene block copolymer

in a liquid state at room temperature is used, the above-mentioned requirement can be satisfied and. . .

SUMM Accordingly, the object of the present invention is to provide a **cyclosporin**-containing pharmaceutical composition characterized in that it comprises **cyclosporin**; **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer as a hydrophilic cosurfactant; an oil component; and a **surfactant**.

SUMM . . . hard gelatin capsule preparation sealed with gelatin bending at the conjugated portion or an oral liquid preparation, prepared from the **cyclosporin**-containing pharmaceutical composition as defined above.

DRWD FIG. 3 is a DSC and DDSC graph of the shell of soft gelatin capsule in which **propylene carbonate** is filled, after storage for 3 months according to Experiment 1; and

DRWD FIG. 4 is a graph showing the **cyclosporin** level in whole blood after administration of the **cyclosporin**-containing pharmaceutical composition prepared according to the present invention (test preparation) in comparison with that of the commercial **cyclosporin** preparation (Sandimmun Neoral®: comparative preparation), in which denotes the **cyclosporin** level in whole blood after administration of the comparative preparation and denotes the **cyclosporin** level in whole blood after administration of the test preparation.

DETD The present invention relates to a **cyclosporin**-containing pharmaceutical composition characterized in that it comprises **cyclosporin**; **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer as a hydrophilic cosurfactant; an oil component; and a **surfactant**. This composition can improve various problems involved in the prior art as mentioned above when it is formulated in the. . .

DETD More specifically, the present invention relates to a pharmaceutical composition containing (1) **cyclosporin** as an active ingredient, (2) **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature as a hydrophilic cosurfactant, (3) one of medium chain triglyceride and mono- and di-glyceride or a mixture thereof as an oil component, and (4) a **surfactant**.

DETD The first essential component of the **cyclosporin**-containing pharmaceutical composition according to the present invention is **cyclosporin** as an active ingredient. **Cyclosporin** is a cyclic peptide compound consisting of 11 amino acids and having a pharmacologically useful activity, i.e. immunosuppresive activity. Although **cyclosporin** A, B, C, D and G depending on the structure of constituent amino acids can be used as the **cyclosporin** component in the present invention, **cyclosporin** A is mostly preferred since its pharmacological activity and clinical indication and effectiveness are well established in the art.

DETD . . . of the composition of the present invention is a hydrophilic cosurfactant. The hydrophilic cosurfactant which can be used in the **cyclosporin**-containing pharmaceutical composition of the present invention includes **propylene carbonate** or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature.

DETD As one of the cosurfactant which can be used in the present invention, **propylene carbonate** is a colorless transparent liquid and has a chemical name (±)-4-methyl-1,3-dioxolan-2-one. It has been used as a solvent for the pharmaceutical preparations for oral and topical administration. The chemical structure of **propylene carbonate** is represented by the following formula (I): ##STR1##

DETD **Propylene carbonate** is a substance which is used as a non-volatile, stable liquid carrier particularly in hard gelatin capsule preparation. In addition,. . . capsules at high temperature and therefore, can ensure the stability of the preparation during storage and production procedures. Further, since **propylene carbonate** does not contain hydroxy group (--OH), it does not have a problem of serious hygroscopic property differently from glycols and also not have a permeability to gelatin capsule shell. Due to the good solubilizing effect of **propylene carbonate** for very slightly soluble drug it can be readily applied to **cyclosporin**.

DETD Another substance which can be used together with **propylene carbonate** as the hydrophilic cosurfactant in the composition of the present invention is polyoxyethylene-polyoxypropylene block copolymer which is liquid at room. . . L43, L101, 31R1, Poloxamer 124, etc., with Poloxamer 124 which is pharmaceutically acceptable being preferably used as the mixture with **propylene carbonate**. Poloxamer 124 is also available under trade name Lutrol or Pluronic L14, Synperonic PE L44, etc. Poloxamer is a hydrophilic, high molecular **surfactant** having molecular weight of 2000 to 18000 and can be used as solubilizer for medicinal component, lipid **emulsion**, ointment base, binder or coating agent for tablets, gelling agent, etc. Although poloxamers have different properties depending on their series,. . . propylene glycol or xylene, contary to other poloxamers. In addition, in comparison with the other solvent used for formulation of **cyclosporin** in the prior art poloxamer has no hygroscopic property and therefore, does not cause the change in the constitutional ratio. . .

DETD As the cosurfactant in the present invention, either **propylene carbonate** alone or a mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature can be used. When the mixture of **propylene carbonate** and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature is used as the hydrophilic copolymer in the present. . .

DETD In the **cyclosporin**-containing pharmaceutical composition according to the present invention, the ratio of the hydrophilic cosurfactant to **cyclosporin** is preferably in the range of 1:0.5-5, more preferably 1:1-3, on the basis of weight.

DETD The use of the above-defined hydrophilic cosurfactant selected according to the present invention in the **cyclosporin**-containing preparation can provide a solubilizing effect sufficient for **cyclosporin** and also provide some advantages that the selected cosurfactant does not cause the change in capsule appearance and the precipitation of active ingredient **cyclosporin** due to the change in solvent content, reduces the manufacturing cost to provide an economical effect and does not have. . .

DETD . . . density of 0.94-0.95, which is higher than the density of vegetable oils and near to the density of water, the **emulsion** using this triglyceride oil component is more stable than the general **emulsion**. In addition, the medium chain triglyceride has lower hydrophobic property than vegetable oils and its solubilizing effect to the active. . . as high as 10% and which has very low polarity and therefore, is very slightly soluble in water, for example, **cyclosporin**. Such medium chain triglyceride has been commercialized under trade name Sefol 860, Sefol 870, Sefol 880, Miglyol 810, Miglyol 812,. . .

DETD . . . acid in which monoglyceride is contained in the ratio of at least 40%. In order to control the absorption of **cyclosporin**, it is more preferable that the mono- and di-glyceride contain monoglyceride of C.sub.18 fatty acid as the main component, which. . .

DETD In the **cyclosporin**-containing pharmaceutical composition of the present invention, the constitutional ratio of the oil component to

cyclosporin is preferably 1:0.5-5, more preferably 1:1-3, on the basis of weight.

DETD The fourth essential component in the **cyclosporin**-containing pharmaceutical composition according to the present invention is a **surfactant**. As the **surfactant** in the composition, any pharmaceutically acceptable **surfactant** can be used, if it is pharmaceutically acceptable, is miscible with the oil component and the hydrophilic cosurfactant component to form an **emulsion** under mild stirring in the external phase and can adjust the particle diameter in the inner phase to 100 nm or below by controlling the constitutional ratio thereof. The **surfactant** which can be preferably used for this purpose includes polyoxyethylene glycolated natural or hydrogenated vegetable oils, polyoxyethylene sorbitan fatty acid. . . polyethylene glycol mono- and di-fatty acid esters, transesterification product of natural vegetable oil triglyceride with polyalkylene polyol, etc. More preferable **surfactant** is polyethylene glycol mono- and di-fatty acid esters commercialized under trade name Solutol (BASF), polyoxyethylene sorbitan fatty acid esters commercialized. . . hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol can be preferably used as the **surfactant**. If the mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol is used as the **surfactant**, they are present in the mixing ratio of 1:0.1-1, preferably 1:0.1-0.5, on the basis of weight.

DETD In the composition of the present invention, either any one of the above defined **surfactant** alone or a mixture of two or more **surfactants** can be used as the **surfactant**. In the **cyclosporin**-containing pharmaceutical composition of the present invention, the constitutional ratio of the **surfactant** to **cyclosporin** is preferably 1:1-7, more preferably 1:3-7, on the basis of weight.

DETD . . . polyoxyethylene-polyoxypropylene block copolymer which is in a liquid state at room temperature and has an emulsifying property, in combination with **propylene carbonate** can be used as the hydrophilic cosurfactant. As previously described, it was already disclosed that when the microemulsion is prepared using the **surfactant** and the cosurfactant having more hydrophilic property than the **surfactant**, the microemulsion can be produced under various conditions and the microemulsion thus produced has an excellent stability. In view of this, the composition of the present invention uses as the hydrophilic cosurfactant poloxamer 124 which is more hydrophilic **surfactant**, together with the **surfactant** component and therefore, can readily form a microemulsion in comparison to the prior preparations using ethanol, propylene glycol, transcutol, glycofurol, dimethylisosorbide, etc. which act merely as the solvent and have practically no emulsifying property. Therefore, the **cyclosporin**-containing pharmaceutical composition according to the present invention can form a more advantageous and stable microemulsion under the patient's variable gastro-intestinal conditions in comparison to the microemulsion **preconcentrate** of the prior art.

DETD In the composition according to the present invention, four essential components are present preferably in the ratio of **cyclosporin** :hydrophilic cosurfactant:**surfactant**:oil component=1:0.5-5:1-7:0.5-5, and more preferably in the ratio of **cyclosporin** :hydrophilic cosurfactant:**surfactant**:oil component=1:1-3:3-7:1-3, on the basis of weight. In addition to this composition, the composition illustrated in the following examples can be. . .

DETD The **cyclosporin**-containing pharmaceutical composition according to the present invention can further contain, if necessary, pharmaceutically acceptable additives as conventionally used. Such

additives. . .

DETD . . . capsule preparation, according to the conventional method for preparing soft capsules it can be prepared, for example, by first dissolving **cyclosporin** in the hydrophilic cosurfactant under mild warming, adding the oil component and the **surfactant** to the resulting solution and then uniformly mixing the constituents and then, if necessary, adding the pharmaceutically acceptable additive, and. . .

DETD . . . present invention is formulated into the soft capsule preparation, the soft capsule thus prepared shows a comparable blood level of **cyclosporin** to the commercial **cyclosporin** soft capsules and further, does not cause any change of the preparation in course of time due to the volatilization. . .

DETD **Cyclosporin** Capsule for Oral Administration

DETD

Component	Content (mg/500 mg Cap.)
Cyclosporin	50.0
Propylene carbonate	120.0
Cremophor RH40	250.0
Miglyol 812	80.0

DETD 50 g of **Cyclosporin** was dissolved in 120 g of **propylene carbonate** with stirring and heating. The given amount of oil component and Cremophor RH40 were added to the obtained solution and then stirred until the homogeneous solution is formed. The resulting **cyclosporin**-containing composition was poured to a machine for preparing soft capsule and then encapsulated according to the conventional method to produce the soft capsule preparations. Each capsule contains 50 mg of **cyclosporin**. Alternatively, after the **cyclosporin**-containing composition is prepared as mentioned above, the composition was filled in hard gelatin capsules and the conjugated portion of hard capsules was sealed with a gelatin bending to produce the hard capsules containing 50 mg of **cyclosporin** per capsule.

DETD **Cyclosporin** Soft Capsule for Oral Administration

DETD . . . soft capsule preparations of Examples 2-A to 2-C having the composition described in the following Table 1 were prepared using **propylene carbonate** alone or in combination with polyoxyethylene-polyoxypropylene block copolymer which is liquid at room temperature as the hydrophilic cosurfactant according to. . .

DETD TABLE 1

	Example No. 2-A	2-B	2-C
Constituent	(mg/Cap.)	(mg/Cap.)	(mg/Cap.)
Cyclosporin	50.0	50.0	50.0
Propylene carbonate	100.0	70.0	100.0
Lutrol L44	25.0		
Pluronic L121	45.0		
Cremophor RH40	210.0	175.0	
Labrafil	20.0	195.0	25.0
GMOrphic 80	35.0.	.	.

DETD **Cyclosporin** Soft Capsule for Oral Administration

DETD TABLE 2

	Example No. 3-A	3-B	3-C
Constituent	(mg/Cap.)	(mg/Cap.)	(mg/Cap.)
Cyclosporin	50.0	50.0	50.0
Propylene carbonate	100.0	120.0	120.0

Synperonic PE L44 40.0
Cremophor RH40 250.0 230.0 225.0
GMOrphic 80 60.0 130.0
Sefol 880 100.0 120.0

. . .

DETD **Cyclosporin** Soft Capsule for Oral Administration

DETD

Component	Content (mg/Cap.)
Cyclosporin	50.0
Propylene carbonate	120.0
Miglyol 880	100.0
Solutol HS15	230.0
Tocopherol	1.5
Total	501.5

DETD **Cyclosporin** Solution for Oral Administration

DETD

Component	Content (mg)
Cyclosporin	100.0
Propylene carbonate	250.0
Poloxamer 124	50.0
Cremophor RH40	400.0
Labrafil	200.0
Sefol 880	200.0
ATMOS 300	100.0

DETD According to the same method as Example 1, **cyclosporin** was dissolved and then filled in a suitable container. When this solution is administered, it is diluted with water.

DETD The stability and pharmacological effect of the **cyclosporin** -containing pharmaceutical composition produced by using **propylene carbonate** and poloxamer 124 as the hydrophilic cosurfactant according to the present invention were determined according to the following experiments and. . .

DETD . . . of the preparation influenced by the change in the constitutional ratio of the composition were determined. In this test, the **cyclosporin**-containing preparation using **propylene carbonate** and poloxamer 124 as the hydrophilic cosurfactant according to the present invention was used as the test preparation and the. . .

DETD . . . C., relative humidity 75%/35° C., and drying condition/ normal temperature, respectively. Then, the change in the content of ethanol and **propylene carbonate** in each preparation was measured and compared therewith. For this, the content of **propylene carbonate** was measured by HPLC and the content of ethanol was measured by GC after pretreatment of the aliquot of the. . .

DETD A) **Propylene Carbonate**

DETD . . . ethanol content even in the case of aluminum foil package. In view of this result, it is apparent that the **cyclosporin** -containing pharmaceutical composition using **propylene carbonate** and poloxamer 124 as the hydrophilic cosurfactant, with the exclusion of ethanol, according to the present invention is outstandingly superior. . .

DETD . . . further the reliable therapeutic effect cannot be obtained. Therefore, depending on what kind of hydrophilic cosurfactant is used in the **cyclosporin** preparation the stability of the soft capsule preparation is varied. Hereinafter, the permeability to the gelatin shell of the hydrophilic. . .

DETD . . . the above Table 6, it can be seen that in comparison to the hydrophilic cosurfactant used in the prior art **propylene**

carbonate used as the hydrophilic cosurfactant in the present invention provides at least comparable stability to dimethylisosorbide and is more stable. . .

DETD Accordingly, it is apparent that since **propylene carbonate** used in the present invention does not cause any change in the constitutional ratio of the composition, the preparation produced. . .

DETD

Component	Content (mg/Cap.)
Cyclosporin	100.0
Propylene carbonate	150.0
Poloxamer 124	70.0
Cremophor RH40	370.0
Sefol 880	200.0
Mono-/di-glyceride	120.0
Tocopherol	3.0
Total	1013.0

DETD . . . any food except water. In this test, each dog received the preparation in an amount corresponding to 100 mg as **cyclosporin** and then 50 ml of water. After 4 hours from administration of the preparation, the test animals were allowed to. . .

DETD . . . of the test and comparative preparations to 6 dogs according to the above method, the AUC and blood level of **cyclosporin** for each preparation are described in the following Table 7.

DETD . . . 7, the composition of the present invention shows a substantially comparable bioavailability in dogs to the commercial comparative composition containing **cyclosporin**. Therefore, it is obvious that the preparation according to the present invention can ensure the reliability equivalent to the known. . .

DETD Determination of bioequivalence of the preparation according to the present invention (test preparation) to the **cyclosporin** -containing commercial preparation (comparative preparation) in human subject:

DETD As can be shown from Table 8 and FIG. 4, the **cyclosporin** -containing pharmaceutical composition using **propylene carbonate** and poloxamer 124 as the hydrophilic cosurfactant according to the present invention shows a substantially equivalent absorption pattern of **cyclosporin** in comparison to the commercial preparation according to the prior art. In addition, in the test preparation the error level. . .

DETD From the results of experiments as mentioned above, it is apparent that the **cyclosporin**-containing pharmaceutical composition according to the present invention can ensure the reliable therapeutic pharmacological effect on at least the same level. . .

CLM What is claimed is:

1. A **cyclosporin**-containing pharmaceutical composition, comprising: (1) **cyclosporin**; (2) **propylene carbonate**; (3) Poloxamer 124; (4) (i) a medium chain triglyceride, or (ii) a mixture of a mono- and a di-glyceride, or a mixture of (i) and (ii); and (5) an additional pharmaceutically acceptable **surfactant** other than (2) or (3), wherein the composition is in the form of a micro **emulsion** pre-concentrate suitable for oral administration, the Poloxamer 124 is a liquid at room temperature, and the composition contains (1), the. . .

2. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein (1) is **cyclosporin** A.

3. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein the composition contains (2) and (3) in a weight ratio of 1:0.1-5.

4. The **cyclosporin**-containing pharmaceutical composition according to claim 3, wherein the composition contains (2) and (3) in a weight ratio of 1:0.1-1.

5. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein the medium chain triglyceride is a triglyceride of a C.sub.8 -C.sub.10 fatty acid.

. . .

6. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein the mono- and di- glyceride is a mixture of glycerol mono- and di-. . .

7. The **cyclosporin**-containing pharmaceutical composition according to claim 1, (4) is a mixture of medium chain triglyceride and mono- and di- glyceride in. . .

8. The **cyclosporin**-containing pharmaceutical composition according to claim 7, wherein (4) is a mixture of medium chain triglyceride and mono- and di- glyceride. . .

9. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein (5) is selected from the group consisting of polyoxyethylene glycolated natural vegetable oils,. . .

10. The **cyclosporin**-containing pharmaceutical composition according to claim 9, wherein (5) is selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated. . .

11. The **cyclosporin**-containing pharmaceutical composition according to claim 10, wherein (5) is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and. . .

12. The **cyclosporin**-containing pharmaceutical composition according to claim 11, wherein (5) is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oil and. . .

13. The **cyclosporin**-containing pharmaceutical composition according to claim 1, wherein the composition contains (1), the total amount of (2) and (3), (5) and. . .

14. The **cyclosporin**-containing pharmaceutical composition according to claim 1, further comprising one or more pharmaceutically

acceptable additives selected from the group consisting of. . .
15. The **cyclosporin**-containing pharmaceutical composition according to claim 1, which is in the form of an orally administrable preparation.

16. The **cyclosporin**-containing pharmaceutical composition according to claim 15, wherein the orally administrable preparation is a soft capsule, a hard capsule sealed with. . .
17. A method of orally administering **cyclosporin**, comprising administering to a subject the composition of claim 1.

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TITLE:	**Cyclosporin**-containing pharmaceutical composition
INVENTOR(S):	Kim, Jung Woo, Seoul, Korea, Republic of Shin, Hee Jong, Kyunggi-do, Korea, Republic of Yang, Su Geon, Seoul, Korea, Republic of
PATENT ASSIGNEE(S):	Chong Kun Dang Corp., Seoul, Korea, Republic of (non-U.S. corporation)

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EXEMPLARY CLAIM:	1
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s hydrophilic (20a) lipophilic (20a) (cremophor or poloxamer)
L1 40 HYDROPHILIC (20A) LIPOPHILIC (20A) (CREMOPHOR OR POLOXAMER)

=> d 20-40 kwic, pi

L1 ANSWER 20 OF 40 USPATFULL on STN
DETD [0014] The useful block copolymers of ethylene oxide and propylene oxide herein generally speaking have a **hydrophilic-lipophilic** balance (HLB) value within the range of from 8 to 30, and preferably from 12 to 25. Using the **poloxamer** coding labels of BASF, suitable poloxamers for use in this invention include, but are not limited to:
PI US 2002114798 A1 20020822
US 6548556 B2 20030415

L1 ANSWER 21 OF 40 USPATFULL on STN
DETD . . . and cavitation forces predorninate, in order to convert the drugs into a stable, latex-type microdispersion. Other non-ionic surface-active agents include **poloxamers** such as Pluronic F-68 and Pluronic F-108, Polysorbates 60 and 80, and Triton WR-1339 (**hydrophilic-lipophilic** balance ranging from 12-18). The concentration of the non-ionic surface-active agent ranges from 0% (optional) to 3%. However, the preferred. . .
PI US 2002071870 A1 20020613
US 6555139 B2 20030429

L1 ANSWER 22 OF 40 USPATFULL on STN
SUMM [0067] A **hydrophilic** surfactant selected preferably has a **hydrophilic-lipophilic** balance (HLB) of greater than or equal to 10, for example **Cremophor**®RH40 or EL.
PI US 2002068083 A1 20020606
US 6432445 B2 20020813

L1 ANSWER 23 OF 40 USPATFULL on STN
SUMM (h) block copolymers which are alkoxylated glycols having ethoxylated and propoxylated segments (for example, **Poloxamers** 182 and 234, and Meroxapol 174); wherein the nonionic surfactant is selected so that it has an HLB (**hydrophilic-lipophilic** balance) value in the range of 1-15.
PI US 6387357 B1 20020514

L1 ANSWER 24 OF 40 USPATFULL on STN
DETD . . . the control composition (containing LMW heparin only).
TABLE 1

Composition Components and Amounts

Composition	Components	Weight (mg)
Composition A: Bile Salt + **Hydrophilic** Surfactant + **Lipophilic** Surfactant	Chenodeoxycholate	130
	Cremophor RH40 340	
	Arlacel 186	320
	Propylene glycol	210
	LMW heparin	10
Control 1	LMW heparin	10

DETD . . . present invention, compositions B and D were prepared comprising of LMW heparin, a bile salt and a non-ionic hydrophilic surfactant (**Cremophor**® RH40). In addition, composition C

and E were comprised of a bile salt, the **hydrophilic** surfactant, and a **lipophilic** surfactant (Arlacel® 186). Control compositions for composition B-E include LMW heparin alone (Control 2), LMW heparin with the non-ionic hydrophilic. . . summarized in Table 3 below.

TABLE 3

Composition Components and Amounts

Composition	Components	Weight (mg)
Composition B: Bile Salt + Hydrophilic Surfactant	Ursodeoxycholate	130
	Cremophor RH40	340
	Propylene glycol	210
	LMW heparin	10
Composition C: Bile Salt + **Hydrophilic** Surfactant + **Lipophilic** Surfactant	Ursodeoxycholate	130
	Cremophor RH40	340
	Arlacel 186	320
	Propylene glycol	210
	LMW heparin	10
Composition D: Bile Salt + **Hydrophilic** Surfactant	Chenodeoxycholate	130
	Cremophor RH40	340
	LMW heparin	10
Composition E: Bile Salt + **Hydrophilic** Surfactant + **Lipophilic** Surfactant	Chenodeoxycholate	130
	Cremophor RH40	340
	Arlacel 186	320
	LMW heparin	10
Control 2	LMW heparin	60
Control 3: **Hydrophilic** Surfactant	**Cremophor** RH40	340
	LMW heparin	60
Control 4: **Lipophilic** Surfactant	Arlacel 186	300
	LMW heparin	60

PI US 2001024658 A1 20010927
US 6458383 B2 20021001

L1 ANSWER 25 OF 40 USPATFULL on STN

SUMM . . . to Winterton et al. discloses a conditioning solution for contact lenses that comprises a combination of a poloxamine and a **poloxamer** surfactant each having an HLB (**hydrophilic-lipophilic** balance) of seven or below. The solution according to the invention forms a uniform **hydrophilic** film on a lens surface for which proteins have very little affinity. As such, a contact lens contacted by the. . .

SUMM . . . a factor in determining the emulsification characteristics of a nonionic surfactant. In general, surfactants with lower HLB values are more **lipophilic**, while surfactants with higher HLB values are more **hydrophilic**. The HLB values of various poloxamines and **poloxamers** are provided by BASF Wyandotte Corp., Wyandotte, Mich. Preferably, the HLB of the surfactant in the present invention is at. . .

PI US 6274133 B1 20010814

L1 ANSWER 26 OF 40 USPATFULL on STN

DETD . . . prepared according to the method of Example 1, having a substrate particle, an active ingredient (itraconazole) a mixture of non-ionic **hydrophilic** surfactants (**Cremophor** RH-40 and PEG-150 monostearate), an ionic **hydrophilic** surfactant (sodium taurocholate) and a **lipophilic** surfactant (glycerol monolaurate). The components and their amounts were as follows:

PI US 6248363 B1 20010619

L1 ANSWER 27 OF 40 USPATFULL on STN
SUMM . . . in the compositions of the present invention have a molecular weight of from about 1950 to about 3350 and a **hydrophilic lipophilic** balance (hlb) of from about 10 to about 20. Representative **poloxamers** include **poloxamer** 124 (Pluronic® L44, MW about 2200, hlb 16), Pluronic® 10R5 (MW about 1950, hlb 15), Pluronic® 17R4 (MW about 2650,. . .
PI US 6193954 B1 20010227

L1 ANSWER 28 OF 40 USPATFULL on STN
SUMM . . . and their mixtures. Use might be made of other types of O/W emulsifiers, in particular of those having an HLB (**Hydrophilic Lipophilic** Balance) of greater than 10, such as oxyethylenated nonylphenols, oxyethylenated and/or oxypropylenated block polymers, such as **Poloxamers**, or sorbitan fatty esters.
PI US 6174518 B1 20010116
WO 9913853 19990325

L1 ANSWER 29 OF 40 USPATFULL on STN
DETD This cyclosporin composition contains a digestible oil and a **hydrophilic** surfactant, and also a **lipophilic** surfactant (Imwitor 742) which will reduce the lipolysis-inhibiting effect of the **hydrophilic** surfactant (**Cremophor** RH40) on the digestible oil (Miglyol 812). However, the Imwitor 742 is not incorporated in order to impart these properties. . .
DETD . . . in Table 1, the lipolysis of FCO is strongly inhibited (i.e. 80% inhibition after 60 minutes) when 0.4 parts of **Cremophor** RH40 are added to one part (w/w) of oil. However, following the addition of the **lipophilic** surfactant Crill 1 to this formulation system, the inhibitory effects of the **hydrophilic** surfactant are dramatically reduced. For example, the addition of 1.5 parts Crill 1 to 0.4 parts **Cremophor** RH40 and 1.0 parts (all w/w) FCO reduced the level of lipolysis inhibition after 60 minutes from 80% to less. . .
PI US 6096338 20000801

L1 ANSWER 30 OF 40 USPATFULL on STN
SUMM . . . to Winterton et al. discloses a conditioning solution for contact lenses that comprises a combination of a poloxamine and a **poloxamer** surfactant each having an HLB (**hydrophilic-lipophilic** balance) of seven or below. The solution according to the invention forms a uniform **hydrophilic** film on a lens surface for which proteins have very little affinity. As such, a contact lens contacted by the. . .
SUMM . . . major factor in determining the emulsification characteristics of a nonionic surfactant. In general, surfactants with lower HLB values are more **lipophilic**, while surfactants with higher HLB values are more **hydrophilic**. The HLB values of various poloxamines and **poloxamers** are provided by BASF Wyandotte Corp., Wyandotte, Mich.
PI US 6037328 20000314

L1 ANSWER 31 OF 40 USPATFULL on STN
DETD . . . emulsifier/surfactant useful in combination with polysorbates in the practice of the present invention may be employed and is preferably a **poloxamer** such as **Poloxamer** 407. Polyxamer 407 has an HLB (**hydrophilic/lipophilic** balance) of about 22 and is sold under the tradename Pluoronic-127 (BASF-Wyandotte; Parsippany, N.J.). The two surfactants can be employed. . .
PI US 6001392 19991214

L1 ANSWER 32 OF 40 USPATFULL on STN
DETD . . . surfactants include, without limitation, lecithin-based surfactants, egg yolk phospholipids, and synthetic surfactants such as poloxamers (available commercially as Pluronic® polyols). **Poloxamers** are polyoxyethylene-polyoxypropylene block polymers, which are available in a wide range of molecular weights and HLB (**hydrophilic/lipophilic** balance) values. The currently preferred **poloxamer** is **poloxamer**-188 (also known as Pluronic F68). See, for example, Hammerschmidt et al., "Blood Substitutes" (T. M. S. Chang, ed., Marcel Dekker,. . .
PI US 5989918 19991123

L1 ANSWER 33 OF 40 USPATFULL on STN
SUMM . . . interface (between the W and HC or FC) in the discontinuous emulsified phase often, but not necessarily has a high **hydrophilic-lipophilic** balance (HLB). Preferably the first dispersant is selected from the group consisting of phospholipids, **poloxamers** (such as pluronics), poloxamines (such as tetronics) and sorbitan esters. In particularly preferred embodiments the first dispersant is a phospholipid. . .
PI US 5980936 19991109

L1 ANSWER 34 OF 40 USPATFULL on STN
SUMM . . . is sold by BASF (Parsippany, N.J.) under the name PLURONIC P103 and has a molecular weight of 4950 and a **hydrophilic/ lipophilic** balance (HLB) value of 7-12. **Poloxamer** 334 is sold by BASF under the name PLURONIC P104 and has a molecular weight of 5900 and an HLB. . .
PI US 5912228 19990615

L1 ANSWER 35 OF 40 USPATFULL on STN
DETD **Poloxamer** surfactants in the present invention should have a **Hydrophilic-Lipophilic** Balance (HLB) of between about 10 and about 30, and preferably between about 10 and about 25. Suitable **poloxamers** in this invention include: Poloxamers 105, 108, 123, 124, 183, 184, 185, 188, 215, 217, 234, 235, 237, 238, 284,. . .
PI US 5874479 19990223

L1 ANSWER 36 OF 40 USPATFULL on STN
DRWD This cyclosporin composition contains a digestible oil and a **hydrophilic** surfactant, and also a **lipophilic** surfactant (Imwitor 742) which will reduce the lipolysis-inhibiting effect of the **hydrophilic** surfactant (**Cremophor** RH40) on the digestible oil (Miglyol 812). However, the Imwitor 742 is not incorporated in order to impart these properties. . .
DETD . . . in Table 1, the lipolysis of FCO is strongly inhibited (i.e. 80% inhibition after 60 minutes) when 0.4 parts of **Cremophor** RH40 are added to one part (w/w) of oil. However, following the addition of the **lipophilic** surfactant Crill 1 to this formulation system, the inhibitory effects of the **hydrophilic** surfactant are dramatically reduced. For example, the addition of 1.5 parts Crill 1 to 0.4 parts **Cremophor** RH40 and 1.0 parts (all w/w) FCO reduced the level of lipolysis inhibition after 60 minutes from 80% to less. . .
PI US 5645856 19970708
WO 9524893 19950921

L1 ANSWER 37 OF 40 USPATFULL on STN
SUMM . . . mark: MIGLYOL 812] or linolenic acid monoglyceride [trade mark: MYVEROL 18-92] as an oil component and a surfactant having HLB (**Hydrophilic-lipophilic** balance) value of 10 or more, particularly a reaction product of castor oil and ethylene oxide [trade mark: **CREMOPHOR** RH 40]. In addition, Korean Laid-open Patent

Publication No. 90-4348 (Apr. 12, 1990) discloses a pharmaceutical composition in the form. . .
PI US 5603951 19970218

L1 ANSWER 38 OF 40 USPATFULL on STN
SUMM . . . mark: MIGLYOL 812] or linolenic acid monoglyceride [trade mark: MYVEROL 18-92] as an oil component and a surfactant having HLB (**Hydrophilic-lipophilic** balance) value of 10 or more, particularly a reaction product of castor oil and ethylene oxide [trade mark: **CREMOPHOR** RH 40]. In addition, Korean Laid-open Patent Publication No. 90-4348 (Apr. 12, 1990) discloses a pharmaceutical composition in the form. . .
PI US 5589455 19961231

L1 ANSWER 39 OF 40 USPATFULL on STN
DETD . . . about 1, a water content of less than about 2%, an n.sub.D.sup.60 of about 1.453 to 1.457 and an HLB (**hydrophilic /lipophilic** balance) of about 14 to 16; and **Cremophor** RH60.sup.R, which has a saponification number of about 40 to 50, an acid number of less than about 1, an. . .
PI US 5538997 19960723

L1 ANSWER 40 OF 40 USPATFULL on STN
DETD **Poloxamer** surfactants in the present invention should have a **Hydrophilic-Lipophilic** Balance (HLB) of between about 10 and about 30, and preferably between about 10 and about 25. Suitable **poloxamers** in this invention include: Poloxamers 105, 108, 123, 124, 183, 184, 185, 188, 215, 217, 234, 235, 237, 238, 284,. . .
PI US 4992276 19910212